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| 09/164,568 | 10/01/1998 | RANDOLPH J. NOELLE | 012712-572 | 6823 |

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| EXAMINER |
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GAMBEL, PHILLIP

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| ART UNIT | PAPER NUMBER |
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1644

DATE MAILED: 12/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/164,568

Applicant(s)

NOELLE ET AL.

Examiner

Phillip Gambel

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 August 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 54-56 and 58-68 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 54-56, 58-66, 68 is/are rejected.
- 7) ☒ Claim(s) 67 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission filed on 8/27/04 has been entered.

Applicant's amendment filed 8/27/04 has been entered.

Claims 54-55, 58 and 63 have been amended.

Claims 64-68 have been added.

Claims 54-56 and 58-68, as they read on "autoantigen expressing cells" are being acted upon as the elected invention.

Claims 1-53 and 57 have been canceled previously.

2. This Office Action will be in response to applicant's arguments, filed 8/27/04.

The rejections of record can be found in the previous Office Actions.

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 63-64 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. The specification as originally filed does not provide support for the invention as now claimed: "peripheral blood activated B lymphocyte" (claim 63) and "bone marrow activated B lymphocyte" (claim 64).

Applicant's amendment, filed 8/27/04, directs support to page 10, lines 35-37 and by Example 1 on page 14 of the specification.

However, page 10, paragraph 2 of the instant specification discloses that: "In the case of bone marrow transplantation, the donor bone marrow cells themselves serve as antigen presenting cells contacted with the T cells".

There is no written description of "peripheral blood activated B lymphocyte" and "bone marrow activated B lymphocyte" here.

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Example 1 on page 14 of the instant specification discloses obtaining active B lymphocytes from the spleen and not from the peripheral blood or bone marrow.

The specification as filed does not provide a sufficient written description of bone marrow activated B lymphocyte". The specification does not provide blazemarks nor direction for the instant methods encompassing the above-mentioned "limitation" as currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action

Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above. See MPEP 714.02 and 2163.06

5. Claim 67: It is apparent that MR1 antibody produced by the hybridoma having ATCC Acession No. HB 11048 is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the pertinent cell line / hybridoma which produce this antibody. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

Applicant should amend the specification accordingly (see page 29 of the instant specification).

Affidavits and declarations, such as those under 37 C.F.R. § 1.131 and 37 C.F.R. § 1.132, filed during prosecution of the parent application do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit, the applicant should make the remarks of record in the later application and include a copy of the original affidavit filed in the parent application.

Given the disclosure and the claims (e.g. see claims 5,17 and 29) encompassing the instant MR1 antibody produced by the hybridoma designated ATCC HB 11048 set forth in U.S. Patent No. 5,683,693; the conditions for the deposit of biological materials under 35 USC 112, first paragraph, with respect to MR1 have been satisfied.

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6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 54-56, 58-66 and 68 are rejected under 35 U.S.C. § 103 as being unpatentable over Lederman et al. (U.S. Patent No. 6,403,091) in view of Berschorner et al. (U.S. Patent No. 5,597,563), Cobbold et al. (U.S. Patent No. 5,690,933) and Enyon et al. (J. Exp. Med. 175: 131-138, 1992) for the reasons of record.

Given applicant's amended claims that delete the use of soluble CD40 and soluble CD40 fusion proteins in the claimed methods, the teachings of Armitage et al. (U.S. Patent No. 6,264,951) OR Aruffo et al. (U.S. Patent No. 6,376,459) have been withdrawn from the rejection of record.

Applicant's arguments have been fully considered but are not found convincing essentially for the reasons of record.

Applicant's arguments and the examiner's rebuttal are essentially the same of record.

Applicant argues that the prior art did not provide sufficient motivation and expectation of success at the time the invention was made for the claimed methods.

Applicant argues that Enyon's T cells are not activated and therefore do not express gp39 and therefore is irrelevant to any tolerization process involving T cells expressing gp39 since there would be no need to administer an activated T cell inhibitors if T cells never became activated in the first place due to the lack of co-stimulatory signal. Applicant further asserts that the tolerance taught by Enyon requires the use of an adjuvant and that temporary tolerance as described would be fairly worthless from a therapeutic perspective. Applicant asserts that given the teachings of Enyon, there would be no motivation to administer an anti-gp39 antibody.

Again, Enyon et al. teach that B cell presentation of antigen in the absence of appropriate help leads to antigen-specific T cell anergy in vivo (see entire document). Here, Enyon et al. also acknowledge the art-known role of B cells as APCs, including B cell involvement in tolerance induction in skin graft survival (see page 131, column 2, paragraph 1). Enyon et al. also note that antigen-specific B cells are involved in tolerance induction (page 132, column 1, lines 11-17).

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In contrast to applicant's assertions concerning the limitations of Enyon, the teachings of Enyon et al. are not limited to specific therapeutic regimens. Rather, Enyon et al. does provide sufficient motivation and expectation of success that B cells, including both antigen-specific B cells and small resting B cells can serve as antigen presenting cells in tolerizing regimens. Enyon et al. also teach a role for small B cells as antigen-specific tolerizing antigen-presenting cells in acquired self-tolerance soluble self-proteins (see Abstract and last paragraph of Discussion).

Given that Berschorner's tolerization process is based on depletion of dendritic cells (APCs) in the thymic medulla using an immunosuppressant followed by recruitment or infusion of new APCs to thymus while treating with various stimulating growth hormones, applicant argues that anti-gp39 antibody would have deleterious effects on Berschorner's tolerization process. Applicant asserts that Berschorner teaches away from the claimed methods since Berschorner's methods of not administering an immunosuppressant along with APCs is in direct contravention to the presently claimed methods and further asserts that both methods are mutually exclusive of one another.

Again, Berschorner teach the use of antigen containing antigen-presenting cells for inducing tolerance to autoantigens or self antigens in the treatment of autoimmune diseases by administering the said antigen containing antigen presenting cells and an immunosuppressive (see entire document, including Detailed Description and Claims). Berschorner also teach that the antigen presenting cells include dendritic cells, Langerhans cells and mononuclear phagocytes (see column 6, paragraph 3), encompassed by the claimed methods. While Berschorner is direct to a goal of inducing antigen-specific tolerance while minimizing risk to the animal that is normally associated with protracted immunosuppressive therapy, it is noted that Berschorner acknowledges that immunosuppressive therapy was the standard therapy at the time the invention was made (see Background of the Invention and Summary of the Invention).

Applicant argues that Cobbold's teachings are irrelevant to anti-gp39 antibodies, since these teachings cannot be extrapolated to antibodies against any T cell antigen, particularly to antibodies that inhibit gp39, which were believed to only inhibit T cell's activation of a B cell.

Again, Cobbold et al. teach that specific non-responsiveness can be induced to a self antigen or antigens in order to treat autoimmune diseases by administering immunosuppressive antibodies and antigen (see entire document, including column 3, paragraph 4). Cobbold et al. also note that persistent antigen is require to maintain tolerance, which applies to self (auto) antigens in the treatment of autoimmune diseases (column 3, paragraph 5). Cobbold et al. teach antigen presenting cells can be isolated from the bone marrow, blood, thymus, epidermis, liver, fetal liver or spleen (see column 6, paragraph 3). In contrast to applicant's assertions, Cobbold et al. provides direction to inducing tolerance via the inhibition of T cells. Furthermore, the CD40L was not known at the priority date of Cobbold et al.

Applicant argues that the each and every one of the anti-gp39 antibodies have any effect on T cell responsiveness and asserts that these references only teach anti-gp39 antibodies may reduce B cell activation.

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In contrast to applicant's assertions, Lederman et al. provides for methods for inhibiting the rejection of transplant organs (see column 11, paragraph 6 and Claims) in a subject with 5c8-specific antibodies (i.e. CD40 ligand- / gp39-specific antibodies) in addition to methods of the autoimmune response (see column 11, paragraph 7).

Applicant submit that the combination of references is incongruent and fails to teach the methods of the present claims.

Contrary to applicant's assertions that teachings of Enyon, Beschorner and Cobbold do not support a general conclusion that APCs can be administered to induce tolerance with gp39-specific antagonists with sufficient motivation and expectation of success at the time the invention was made, the following of record is noted.

It was also known that CD40 the ligand for gp39 (CD40 ligand) is present on other APCs such as dendritic cells, which are intimately involved in the induction of T cell immunity or tolerance. In addition, gp39 was known to be expressed mainly by activated T helper cells and a number of CD8⁺ cells as well. Therefore, it was known that one could use gp39 antagonists to block T cell-mediated activation and that the appropriate in vivo APCs such as B cells and dendritic cells, which express CD40, would be subject to such manipulation. It was well known in the art at time the invention was made that the provision of signal 1 (antigen) in the absence of signal 2 (help) would lead to some form of tolerance rather than immunity.

With respect to applicant's request for the support that "it was well known in the art at the time the invention was made that the provision of signal 1 (antigen) in the absence of signal 2 (help) would lead to some form of tolerance rather than immunity", applicant is invited to look no further than the Background of the Instant specification, including page 2, paragraph 1.

As indicated above, applicant acknowledges that APCs can provide antigen to induce tolerance or specific non-responsiveness in various contexts and systems at the time the invention was made.

Contrary to applicant's assertions, the prior art provide sufficient motivation and expectation of success that providing an immunosuppressive regimen, including antagonistic antibodies, in combination with APCs can induce tolerance or antigen-specific nonresponsiveness.

Here, the teachings of Lederman et al. clearly provide for anti-CD40L (anti-5c8, anti-gp39, anti-CD40 ligand) antibodies to inhibit the immune response in order to treat various disease conditions, such as autoimmunity. These teachings are consistent with the teachings of Enyon, Beschorner and Waldmann to provide APC's to induce tolerance to antigens of interest under the cover of immunosuppression at the time the invention was made.

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In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969).

In response to applicant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case the teachings of the primary references pertaining to the treatment of disease conditions such as autoimmunity and the teachings of the secondary references indicating the success of employing APCs to induce tolerance or specific antigen to solve a similar problem of treating autoimmunity would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art of inducing long term non-responsiveness to autoantigens in such individuals having autoimmunity. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144

A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." In re Gurley, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). General skepticism of those in the art -- not amounting to teaching away -- is also "relevant and persuasive evidence" of nonobviousness. Gillette Co. v. S.C. Johnson & Son, Inc., 16 USPQ2d 1923, 1929 (Fed. Cir. 1990). In effect, "teaching away" is a more pointed and probative form of skepticism expressed in the prior art. In any case, the presence of either of these indicia gives insight into the question of obviousness.

A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." See In re Gurley, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994).

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Here in contrast to applicant's assertions of teaching away by the prior art because the references are directed to alternative tolerance induction regimens, there is insufficient discouragement nor skepticism in the prior art for employing various antigen presenting cells, including those known in the prior art and encompassed by the claimed methods, in the induction of tolerance to antigens of interest, including autoantigens. Furthermore, various immunosuppressive regimens associated with tolerance induction regimens were known and practiced at the time the invention was made to achieve this highly desirable goal.

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to select the combination of an autoantigen containing antigen presenting cells and a gp39-specific antibody to induce antigen-specific non-responsiveness to autoantigens as a treatment for autoimmunity by providing persistent autoantigens under the cover of immunosuppressives, since both contribute to long term antigen non-responsiveness in the treatment of autoimmunity.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have not been found persuasive.

8. No claim is allowed.

Claim 67 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
November 22, 2004

